

Claims:

1. A method for identifying an inverse agonist of a CB receptor, the method comprising:
measuring the activity of a constitutively active CB receptor;
- 5 contacting a CB receptor test inhibitory agent with the constitutively active CB receptor; and
measuring the activity of the constitutively active CB receptor following contact with the
inhibitory agent, wherein a decrease in the activity in the constitutively active CB receptor,
compared to the activity of the constitutively active CB receptor in the absence of the
inhibitory agent, indicates that the agent is an inverse agonist.
10
2. A method for determining if a CB receptor inhibitory agent is an inverse agonist or a
true antagonist of a CB receptor, the method comprising:
identifying a test CB receptor inhibitory agent;
contacting the agent with a wild-type CB receptor in the presence of a CB receptor agonist;
15 contacting the agent with a constitutively active CB receptor;
measuring the activity of the wild-type CB receptor and the constitutively active CB receptor,
wherein:
 - (i) a decrease in the activity in both the wild-type CB receptor and the constitutively
active CB receptor indicates that the agent is an inverse agonist, or
 - 20 (ii) a decrease in the activity in the wild-type CB receptor, but not of the activity of the
constitutively active CB receptor, indicates that the compound is a true antagonist.
3. A method for identifying an inverse agonist of a CB receptor, the method comprising:
measuring the activity of a constitutively active CB receptor expressed in a cell;
- 25 contacting a CB receptor test inhibitory agent with the cell expressing the
constitutively active CB receptor; and
measuring the activity of the constitutively active CB receptor following contact with the
inhibitory agent, wherein a decrease in the activity in the constitutively active CB receptor
compared to the activity of the constitutively active CB receptor in the absence of the
30 inhibitory agent indicates that the agent is an inverse agonist.
4. A method for determining if a CB receptor inhibitory agent is an inverse agonist or a
true antagonist of a CB receptor, the method comprising:

identifying a test CB receptor inhibitory agent;

contacting the agent with a cell expressing a wild-type CB receptor in the presence of a CB agonist;

contacting the agent with a cell expressing a constitutively active CB receptor;

5 measuring the activity of the wild-type CB receptor and the constitutively active CB receptor, wherein

- (i) a decrease in the activity in both the wild-type CB receptor and the intrinsic activity of the constitutively active CB receptor indicates that the agent is an inverse agonist; or
- (ii) a decrease in the activity in the wild-type CB receptor, but not the activity of the

10 constitutively active CB receptor, indicates that the compound is a true antagonist

5. The method of any of claims 1, 2, 3, or 4 wherein the constitutively active CB receptor is a CB1 receptor, or a variant thereof, CB2 receptor, or variant thereof.

15 6. The method of any of claims 2 or 4, wherein the wild-type CB receptor is a CB1 receptor, or a variant thereof, CB2 receptor, or variant thereof.

7. The method of claim 5, wherein the constitutively active CB1 receptor is a human CB1 receptor comprising an alanine at position 213.

20

8. The method of claim 5, wherein the constitutively active CB1 receptor is a human CB1 receptor comprising an alanine at position 338.

9. The method according to any of claims 3 or 4, wherein the cell is a mammalian cell,

25 an insect cell, or a yeast cell.

10. The method according to any of claims 2 or 4 wherein the CB agonist is CP55940 or HU210.

30 11. A true antagonist or an inverse agonist identified by the method of any one of claims 1 to 4 for use as a medicament.

12. A pharmaceutical formulation comprising a true antagonist or an inverse agonist as identified by the method of any one of claims 1 to 4, and a pharmaceutically acceptable adjuvant, diluent or carrier.
- 5 13. Use of a true antagonist or inverse agonist as identified by the method of any one of claims 1 to 4 in the preparation of a medicament for the treatment or prevention of a disorder associated with a CB receptor.
14. The use of claim 13, wherein the disorder is obesity.

10

15. A method of treating a CB associated disorder comprising administering a pharmacologically effective amount of the true antagonist or inverse agonist as identified by the method of any one of claims 1 to 4 to a patient in need thereof.
- 15 16. The method of claim 15, wherein the disorder is obesity.
17. A constitutively active CB receptor.
18. The receptor of claim 17, wherein the receptor is a human CB1b receptor.

20

19. The method of claim 18, wherein the receptor comprises an alanine at position 213 of the human wild type CB1b receptor.
- 20 25. The method of claim 18, wherein the receptor comprises an alanine at position 338 of the human wild type CB1b receptor.
21. An isolated nucleic acid sequence comprising a nucleotide sequence that encodes a variant cannabinoid receptor protein wherein one or both of the amino acids located at position 3:49 and 6:32 have been substituted for by another amino acid so as to create a 30 constitutive variant form of the cannabinoid receptor.
22. The isolated nucleic acid according to claim 22, wherein the cannabinoid receptor protein is human CB1 receptor.

23. The isolated nucleic acid according to claim 22, wherein one or both of the amino acids at positions 213 and 338 of CB1 receptor protein is an alanine residue.

24. The isolated nucleic acid sequence according to claim 22 or 23, wherein the sequence 5 comprises the sequence according to any of SEQ ID NO: 2, 3 or 4.

25. A vector comprising the nucleic acid molecule as claimed in any of claims 21-24.

26. A cell or cell line transformed with the vector of claim 25 or the nucleic acid of any of 10 claims 21-24.

27. The cell or cell line according to claim 26, which is a bacterial, yeast, insect or mammalian cell or cell line.

15 28. An isolated cannabinoid receptor polypeptide wherein one or other or both of the natural amino acids at positions 3:49 and 6:32 of the protein have is substituted for another amino acid.

29. The isolated polypeptide of claim 28; wherein the cannabinoid receptor is CB1.

20 30. The isolated polypeptide of claim 29 wherein one or both of the amino acids at positions 3:49 and 6:32 of CB1 is an alanine residue.

31. An isolated human cannabinoid 1 receptor polypeptide comprising the sequence 25 according to SEQ ID NO: 1 wherein the amino acid at position 213 or 338 may be an aspartic acid residue.